

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of

David Reginald ADAMS et al.

Serial No. 09/600,631

Filed: February 12th, 2001

For: AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

Attorney Docket No. 040283-0182

Group Art Unit: 1626

Examiner: R. Anderson

**DECLARATION UNDER 37 CFR § 1.132**  
**OF NATHANIEL JULIUS MONCK**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Nathaniel Julius Monck, the undersigned, a citizen of Great Britain and a resident of Wokingham, United Kingdom, do hereby declare that:

1. I am one of the co-inventors of the invention described in the above-identified patent application entitled "AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS" which was given United States Serial No. 09/600,631, and accordingly I am familiar with the content of the present application.

2. I graduated as a Bachelor of Science from University of Bristol in 1990, and completed a Doctoral Degree from Imperial College, London University in 1993.

3. Since August 1996, I have been employed by VERNALIS RESEARCH LIMITED, assignee of the above-identified application, where I have been engaged in research and development of drugs useful in the treatment of CNS disorders, particularly anxiolytics.

4. I attach my Curriculum Vitae.

5. It is my understanding that the Examiner considers that the claimed subject-matter is obvious over GB-872447 and EP-0194112, and one of the reasons for the objection is that the comparative data submitted to date relate only to Example 20 of the present application. However, there is a considerable amount of additional data previously collected

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which demonstrate that the compounds claimed in the present Application are unexpectedly superior over those of this prior art. These Experiments were carried out by me or under my direct supervision. The experimental results are presented in Table 1 below. The Table contains data which were not originally presented in the specification as filed, and relate to specific Examples already included in the present application, as well as to prior art compounds which contain an unsubstituted aryl group.

Table 1 : Antagonism of 3-MPA-Induced Seizures

Compound	SC	SV
1-carbamoyl-3-phenylazetidine (GB-872447)	22.9	18.5
1-carbamoyl-3-naphthylazetidine	22.9	18
Example 11; R <sup>1</sup> = 3,4-dichlorophenyl	42.8	22.1
Example 12; R <sup>1</sup> = 3,4-dichlorophenyl	45.8	22.1
Example 13; R <sup>1</sup> = 3,4-dichlorophenyl	31.5	13.6
Example 16; R <sup>1</sup> = 4-trifluoromethylphenyl	44.2	13.6
Example 17; R <sup>1</sup> = 3-trifluoromethylphenyl	129.7	15.6
Example 18; R <sup>1</sup> = 3-trifluoromethylphenyl	54.6	15.6
Example 23; R <sup>1</sup> = 3-chloro-4-fluorophenyl	27.2	13.6
Example 25; R <sup>1</sup> = 3,4-difluorophenyl	45.8	17.7
Example 26; R <sup>1</sup> = 3-chloro-4-fluorophenyl	49.9	16.2
Example 28; R <sup>1</sup> = 3-trifluoromethyl-4-fluorophenyl	94.4	17.7
Example 29; R <sup>1</sup> = 3-chlorophenyl	129.3	18.6

SC = seizure threshold after treatment with test compound

SV = seizure threshold in vehicle treated group

6. The data in the Table show that the compounds of the present invention exhibit a significant improvement over the unsubstituted prior art compounds since they significantly increase the dose of 3-MPA to initiate a seizure response. Thus, it is reasonable to conclude that the compounds of the invention which contain a substituted aryl group are unexpectedly more potent anti-convulsant agents than compounds which contain an

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unsubstituted aryl group. I consider that this improvement could not have been predicted, whether in view of GB-872447 or a combination of GB-872447 and EP-0194112.

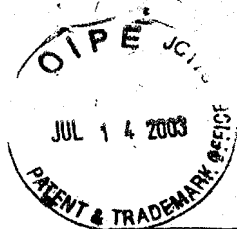
I further declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date:

4<sup>th</sup> July 2003

Nathaniel Julius Monck

Nathaniel Julius Monck



**Nathaniel Julius Thomas Monck**

10 Park Crescent, Sunningdale, Berkshire, SL5 0AX, UK.

Date of Birth: 16 July 1968

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**Professional Experience:**

Aug 1996-present date

**Vernalis Research Ltd**, Winnersh Triangle.

Principal Scientist, Chemistry Dept.

Anxiety Project Leader (chemistry) 1997-2001

Sodium Channel Project Leader (chemistry) 2001-present date

Feb 1996-Aug 1996

**SmithKline Beecham**, Harlow.

Industrial post-doctoral position.

Synthesis of conformationally restricted unnatural amino-acids and incorporation into peptide mimetic libraries via combinatorial chemistry.

Feb 1995-Nov 1995

**The Australian National University**, Canberra, ACT.

Post-Doctoral Research Fellow

Research Advisor: Professor Lewis N. Mander, FRS

Studies towards the total synthesis of gibberellic acid GA<sub>103</sub>, the total synthesis of Harringtonolide and the partial synthesis of 7 $\beta$ -hydroxy-kaur-16-en-19-oic acid.

Jan 1994-Jan 1995

**The Ohio State University**, Columbus, Ohio.

Post-Doctoral Research Fellow

Research Advisor: Professor Leo A. Paquette

Studies towards the total synthesis of Jatrophatriene.

Oct 1990-Dec 1993

**Imperial College**, University of London.

Research Fellow; Research Advisor: Professor Steven V. Ley, FRS

Development of new synthetic methods for the total synthesis of Milbemycin  $\alpha_1$  and Nemadectin  $\beta$  utilising relay studies of Nemadectin  $\gamma$ .

Undergraduate Teaching Assistant; supervision and demonstration of laboratory experiments.

Oct 1992-Dec 1992

**Rhône-Poulenc-Rorer**, Dagenham.

Research Fellow; Research Advisor: Dr Michael Ashton

CASE award industrial placement.

Jul 1989-Aug 1989

**Institute of Child Health/Great Ormond Street Hospital**, London.

Research Assistant; Research Advisor: P. Bird.

Studies towards the development of HPLC methods for the analysis of samples from neurofibrosarcoma patients.

### Awards/Honours:

- 1997-1998 MRSC CChem awarded as result of Structured Assessment.  
1990-1993 CASE Award from Rhône-Poulenc-Rorer.

### Courses:

- Dec 1998 Introduction to Molecular Modelling, including the use of Legion, Selector, Flexidock and Gasp operations; Tripos Inc., Milton Keynes  
July 1997 Medicinal Chemistry Residential Course: An introduction to the pharmaceutical industry. RSC, Canterbury.

### Education:

- 1990-1993 Imperial College, University of London  
PhD, DIC, Synthetic Organic Chemistry  
Research Advisor: Professor Steven V. Ley, FRS  
Dissertation: Studies towards the Total Synthesis of the Milbemycins.  
1987-1990 University of Bristol,  
Bachelor of Science (Hons), Chemistry, First class.  
Final year project supervisor: Dr Thomas V. Lee  
Dissertation: The Use of Enzymes in Organic Media.  
1979-1986 Acland Burghley Comprehensive School, London  
A-levels: Chemistry (A), Mathematics (B), Physics (A)  
O-levels: French, History, Geography, Music, Chemistry, Physics, Mathematics, Advanced Mathematics, English Literature, English Language.

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**Preparation of azetidine carboxamides for the treatment of CNS disorders.** Snape, Mike Frederick; Fletcher, Allan; Stanhope, Kelly Jean; Monck, Nathaniel Julius. (Vernalis Research Limited, UK). - PCT Int. Appl. (2001), 39 pp. CODEN: PIXXD2 WO 0107043 A1 20010201.

**Preparation of azetidine-1-carboxamide derivatives as neuroprotectants.** Snape, Mike; Monck, Nathaniel Julius; Fletcher, Allan; Stanhope, Kelly Jean; Mansell, Howard Langham; Nelson, Alan John. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 31 pp. CODEN: PIXXD2 WO 0107023 A2 20010201.

**2-adamantanemethanamine compounds for treating abnormalities in glutamatergic neurotransmission, and preparation thereof.** Gillespie, Roger John; Monck, Nathaniel Julius Thomas; Bird, Andrew James; Ward, Simon Edward. (Vernalis Research Limited, UK). PCT Int. Appl. (2000), 35 pp. CODEN: PIXXD2 WO 0044371 A1 20000803.

**3,5-Disubstituted-4-hydroxyphenyls Linked to 3-Hydroxy-2-methyl-4(1H)-pyridinone: Potent Inhibitors of Lipid Peroxidation and Cell Toxicity.** Bebbington, David; Monck, Nathaniel J. T.; Gaur, Suneel; Palmer, Alan M.; Benwell, Karen; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Departments of Chemistry and Molecular Pharmacology, Cerebrus, Wokingham, UK. *Journal of Medicinal Chemistry* (2000), 43(15), 2779-2782.

**Dual-mechanism antioxidants: Novel neuroprotective compounds--II.** Bebbington, David; Gaur, Suneel; Dawson, Claire E.; Monck, Nathaniel J. T.; Palmer, Alan M.; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Department of Chemistry, Cerebrus, Wokingham, UK. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-093.

**Synergistic dual-mechanism antioxidants: Novel neuroprotective compounds--I.** Bebbington, David; Monck, Nathaniel J. T.; Gaur, Suneel; Palmer, Alan M.; Benwell, Karen R.; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Department of Chemistry, Cerebrus, Wokingham, UK. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-092.

**Preparation of indolinealkylamine derivatives as 5-HT<sub>2B</sub> and/or 5-HT<sub>2C</sub> receptor ligands.** Adams, David Reginald; Bentley, Jonathan Mark; Roffey, Jonathan Richard Anthony; Hamlyn, Richard John; Gaur, Suneel; Duncton, Matthew Alexander James; Bebbington, David; Monck, Nathaniel Julius; Dawson, Claire Elizabeth; Pratt, Robert Mark; George, Ashley Roger. (Cerebrus Pharmaceuticals Limited, UK; et al.). *PCT Int. Appl.* (2000), 81 pp. CODEN: PIXXD2 WO 0012475 A1 20000309.

**Preparation of 2-adamantanecarboximidamides NMDA receptor antagonists.** Monck, Nathaniel Julius Thomas; Gillespie, Roger John; Bird, Andrew James. (Cerebrus Limited, UK). *PCT Int. Appl.* (1999), 34 pp. CODEN: PIXXD2 WO 9938841 A1 19990805.

**Azetidinecarboxamide derivatives for the treatment of CNS disorders.** Adams, David Reginald; Cliffe, Ian Anthony; Mansell, Howard Langham; Monck, Nathaniel Julius. (Cerebrus Limited, UK). *PCT Int. Appl.* (1999), 38 pp. CODEN: PIXXD2 WO 9937614 A1.

**Azetidinecarboxamide derivatives for treating CNS disorders.** Shepherd, Robin Gerald; Adams, David Reginald; Bentley, Jon; Bodkin, Corinna Dagmar; Cliffe, Ian Anthony; Davidson, James Edward Paul; Mansell, Howard Langham; Monck, Nathaniel Julius. (Cerebrus Limited, UK; Shepherd, Joy, Miriam). *PCT Int. Appl.* (1999), 46 pp. CODEN: PIXXD2 WO 9937613 A1.

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**Preparation of ortho-hydroxypyridinone derivatives as iron chelating and antioxidant agents.** Bebbington, David; Monck, Nat; Gaur, Suneel; Palmer, Alan; Porter, Richard; Malcolm, Craig. (Cerebrus Limited, UK). *PCT Int. Appl.* (1999), 68 pp. CODEN: PIXXD2 WO 9923075 A1 19990514.

**Studies Directed toward the Synthesis of the Unusual Antileukemic Diterpene Jatrophastrione. 2. Functionalization of Advanced Polycyclic Precursors to the 9-Epi and 8,9-Dehydro Congeners.** Paquette, Leo A.; Edmondson, Scott D.; Monck, Nathaniel; Rogers, Robin D. Evans Chemical Laboratories, The Ohio State University, Columbus, OH, USA. *J. Org. Chem.* (1999), 64(9), 3255-3265.

**Synthetic and structural studies on novel gibberellins.** Pour, Milan; King, Geoffrey R.; Monck, Nathaniel J. T.; Morris, Jonathan C.; Zhang, Hongbin; Mander, Lewis N. Research School of

Chemistry, Inst. of Advanced Studies, Australian National Univ., Canberra, Australia. Pure Appl. Chem. (1998), 70(2), 351-354.

**A New and Efficient Strategy for the Total Synthesis of Polycyclic Diterpenoids: The Preparation of Gibberellins ( $\pm$ )-GA103 and ( $\pm$ )-GA73.** King, Geoffrey R.; Mander, Lewis N.; Monck, Nathaniel J. T.; Morris, Jonathan C.; Zhang, Hongbin. Research School of Chemistry, Australian National University, Canberra, Australia. J. Am. Chem. Soc. (1997), 119(16), 3828-3829.

**Total synthesis of the spiroketal macrolide (+)-milbemycin  $\alpha$ 1.** Ley, Steven V.; Madin, Andrew; Monck, Nathaniel J. T.. Univ. Chem. Lab., Cambridge, UK. Tetrahedron Lett. (1993), 34(46), 7479-82.